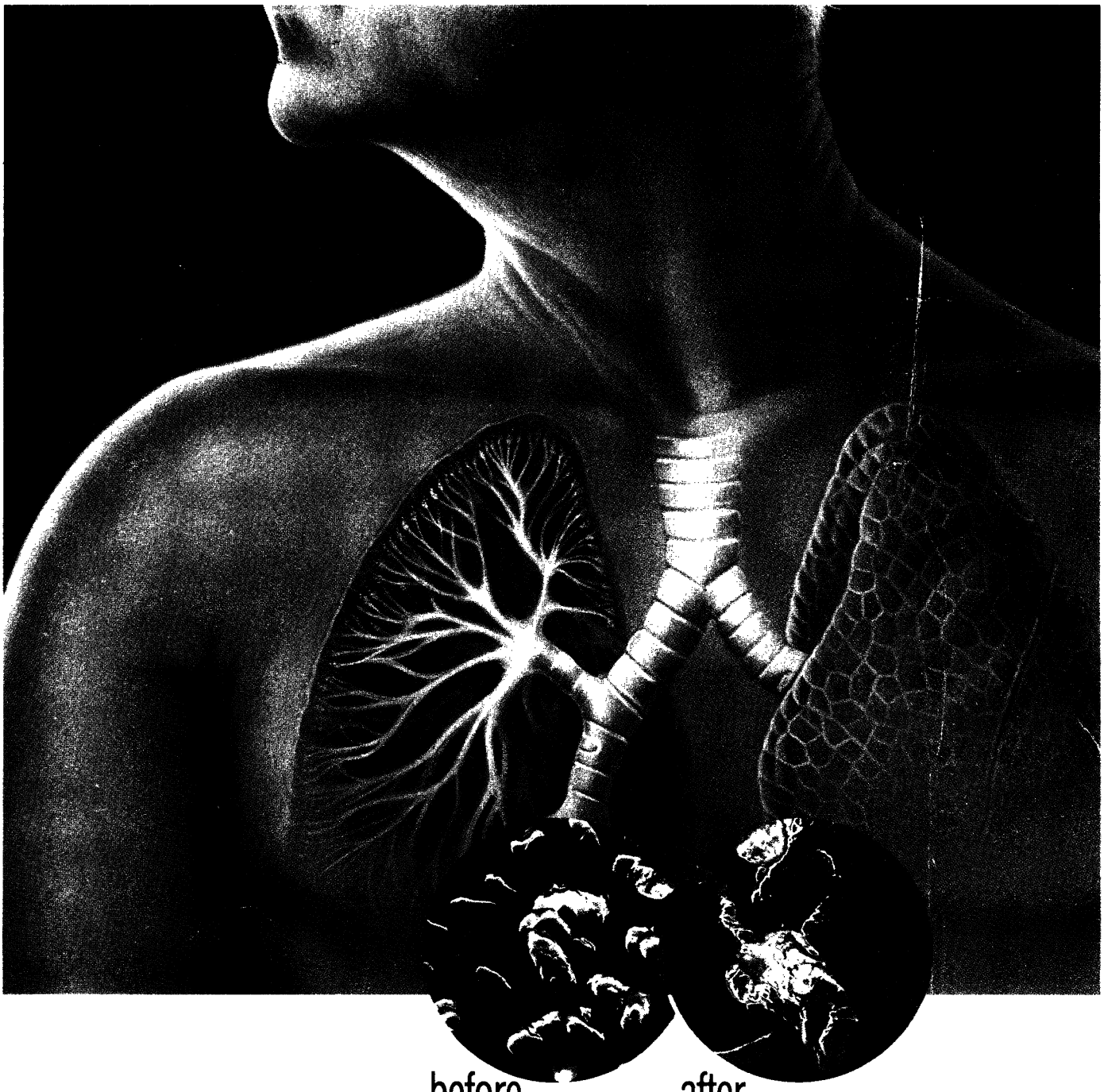
Strong on results.



before Color-enhanced photo of *H. influenzae* seen through a scanning electron microscope.[5]

after *H. influenzae* culture after 24 hours' incubation with Bactrim (trimethoprim and sulfamethoxazole/Roche) at 5 × MIC. Note long filaments and distorted shapes of bacteria.

ROCHE®

Simple to take.

In acute exacerbations of chronic bronchitis

- Clears susceptible pathogens from sputum[1-4]
- Reduces cough and sputum volume[1-4]
- Reduces evidence of inflammation[1]

Bactericidal *in vitro* against *H. influenzae* (nontypable strains)

Bactrim shows high activity *in vitro* against most strains of *H. influenzae*—even ampicillin-resistant strains. However, *in vitro* data do not necessarily correlate with clinical results.
In morphologic studies,[5] cultures of *H. influenzae* were exposed to Bactrim at 5× MIC. After just four hours, bacteria began to form filaments, indicating an alteration in the normal pattern of cell division. After 12 hours, virtually all bacteria had formed filaments. When these bacteria were removed and recultured in drug-free nutrient medium, almost all were unable to divide and form colonies—a result interpreted as demonstrating that, at the above concentration, the effect of Bactrim on the *H. influenzae* was bactericidal.

Also effective against susceptible strains of *S. pneumoniae in vitro*

In sputum cultures of *S. pneumoniae,* 91% of strains were susceptible to Bactrim.[6]
In acute exacerbations of chronic bronchitis involving *S. pneumoniae* or *H. influenzae,* sputum cultures taken seven days after a two-week course of therapy showed that Bactrim eradicated these bacteria in 91% (50 of 55) of the patients treated.[5]

Effective—and economical—antimicrobial therapy

In three double-blind studies, Bactrim DS *b.i.d.* was unsurpassed by ampicillin *q.i.d.*[1-3]
And in ten clinical comparisons with tetracycline involving nearly 700 patients, Bactrim proved comparable on major clinical parameters: change in sputum purulence, reduction in sputum volume and microbiological clearance of pathogens.[4]
And equally important: the convenient and economical *b.i.d.* dosage of Bactrim DS is designed to encourage patient compliance.

Bactrim™ DS

(trimethoprim and sulfamethoxazole/Roche)

Consistent success on a *b.i.d.* schedule

Please see references and summary of product information on following page.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Wormser GP, Keusch GT, Heel RC: *Drugs 24*:459-518, Dec 1982. 3. Ronald AR: *Clin Ther 3*:176-189, 1980. 4. Rubin RH, Swartz MN: *N Engl J Med 303*:426-432, Aug 21, 1980. 5. Cunha BA: *Postgrad Med 70*(6):149-156, Dec 1981. 6. Neu HC: *Infectious Diseases 10*(6):4, 19, Jun 1980. 7. Jones SR: *Ration Drug Ther 13*(11): 1-5, Nov 1979.

Now on Medi-Cal

Potency with fewer problems.

Double-strength TOLECTIN DS has been proved comparable in efficacy to indomethacin...but is often gentler because it offers significantly fewer CNS side effects (dizziness light-headedness).[1]

TOLECTIN DS is also very well suited for long-term therapy.

TOLECTIN DS...instead of indomethacin. A good idea whose time has come.

Note: For rheumatoid arthritis patients classified as Functional Class IV or incapacitated with little or no self-care, safety and effectiveness have not yet been established.

1. Caldwell J, Brandon ML, Franz KB, et al: A double-blind comparison of the efficacy and side effect liability of tolmetin and indomethacin. Presented at a symposium: *Tolectin: A New Non-steroidal Anti-inflammatory Agent*. Washington, DC, April 1975. *Excerpta Medica* 1976, pp 44-57. See warnings, precautions, and side effects sections in brief summary of prescribing information on next page.

TOLECTIN® DS

(TOLMETIN SODIUM) 400 MG CAPSULES

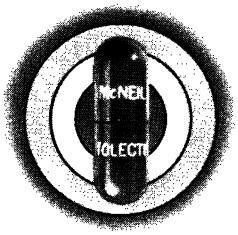
As potent as indomethacin ...often gentler.

Now on Medi-Cal

TOLECTIN® DS

(TOLMETIN SODIUM) 400 MG CAPSULES

As potent as indomethacin...



often gentler.

SUMMARY OF PRESCRIBING INFORMATION
TOLECTIN® DS (tolmetin sodium)
double-strength capsules—for oral administration
Contraindicated: In patients who have previously exhibited intolerance to it; patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.
Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. If TOLECTIN must be given to patients with active peptic ulcer, closely supervise for signs of ulcer perforations or severe gastrointestinal bleeding.
Precautions: *General*—Ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

Renal failure, sometimes acutely associated with nephrotic syndrome has been reported. Closely monitor patients with impaired renal function; they may require lower doses.

TOLECTIN prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when TOLECTIN is administered.

In patients receiving concomitant TOLECTIN-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

TOLECTIN should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g., sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.

As with other nonsteroidal anti-inflammatory drugs, anaphylactoid reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships which exist among nonsteroidal anti-inflammatory drugs, anaphylactoid reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds, particularly zomepirac sodium. Patients who have had anaphylactoid reactions on TOLECTIN should be treated with conventional therapy, such as epinephrine, antihistamines, and/or steroids.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with TOLECTIN. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), discontinue TOLECTIN.

Usage in Pregnancy—Because TOLECTIN has not been studied in pregnant women, use during pregnancy is not recommended.

Nursing Mothers—Because TOLECTIN may be secreted in human milk, nursing should not be undertaken while a patient is on this drug.

Drug Interactions—There have been rare reports that prothrombin time may increase and bleeding may occur.
Adverse Reactions: *Incidence Greater Than 1%*—The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.

Gastrointestinal: Nausea (11%), dyspepsia,* gastrointestinal distress,* abdominal pain,* diarrhea,* flatulence,* vomiting,* constipation, gastritis, and peptic ulcer.

Body as a Whole: Headache,* asthenia,* chest pain

Cardiovascular: Elevated blood pressure,* edema*

Central Nervous System: Dizziness,* drowsiness, depression

Metabolic/Nutritional: Weight gain,* weight loss*

Dermatologic: Skin irritation

Special Senses: Tinnitus, visual disturbance

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred.

Urogenital: Elevated BUN, urinary tract infection

*Reactions occurring in 3% to 9% of patients treated with TOLECTIN. Reactions occurring in fewer than 3% of the patients are unmarked.
Incidence Less Than 1% (Causal Relationship Probable)—*Gastrointestinal:* Gastrointestinal bleeding with or without evidence of peptic ulcer, glossitis, stomatitis, hepatitis, liver function abnormalities

Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy

Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis

Cardiovascular: Congestive heart failure in patients with marginal cardiac function

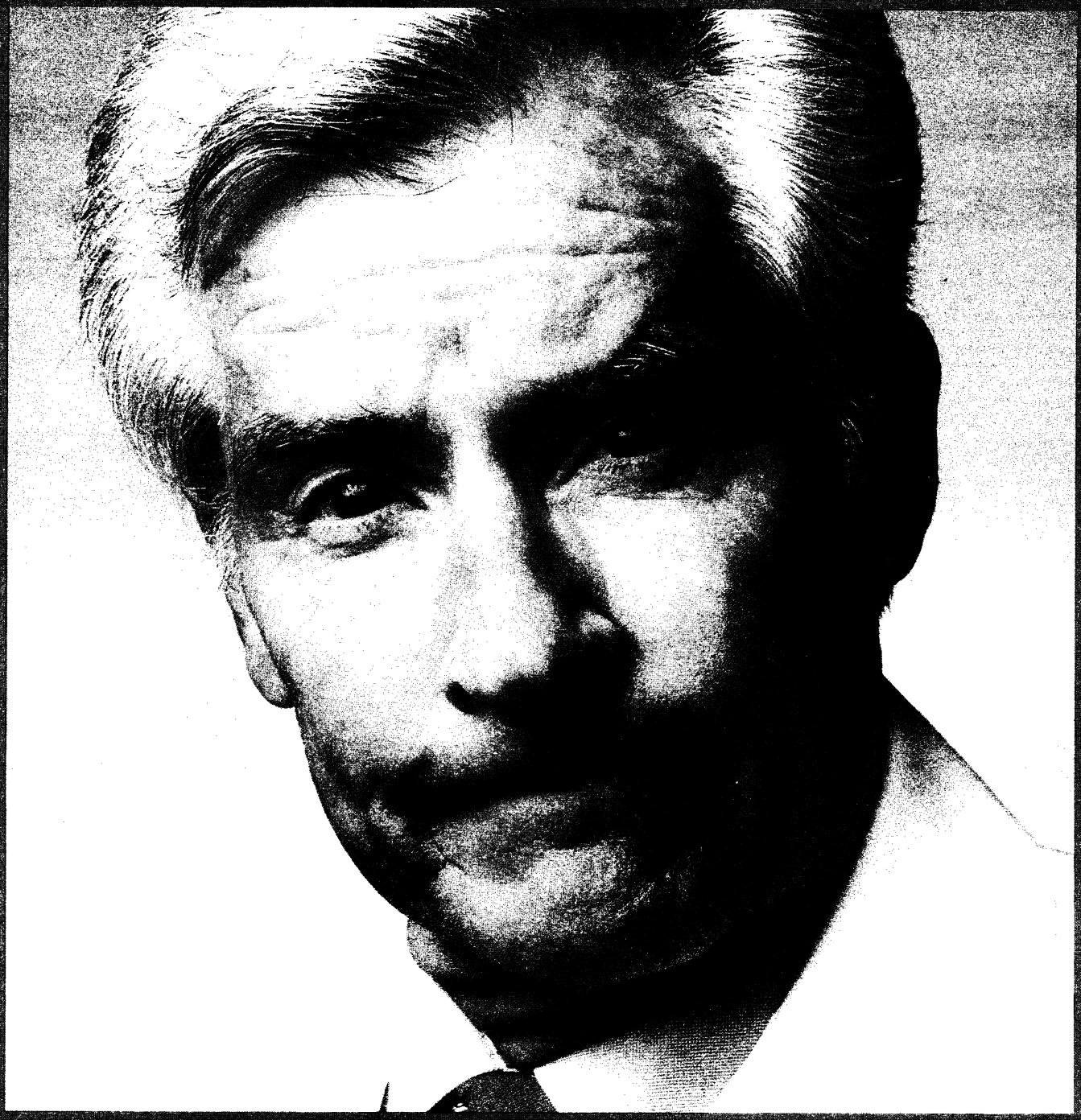
Dermatologic: Urticaria, purpura, erythema multiforme

Urogenital: Hematuria, proteinuria, dysuria, renal failure
Incidence Less Than 1% (Causal Relationship Unknown)—*Body as a Whole:* Epistaxis

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdosage, see full prescribing information.
Also available: TOLECTIN® (tolmetin sodium) tablets 200 mg.: 100's—Military 6505-01-038-7460, VA 6505-01-038-7460A; Capsules 400 mg.: 100's—VA 6505-01-091-9624A.
8/17/83

McNEIL PHARMACEUTICAL
McNEILAB, INC., Spring House, PA 19477



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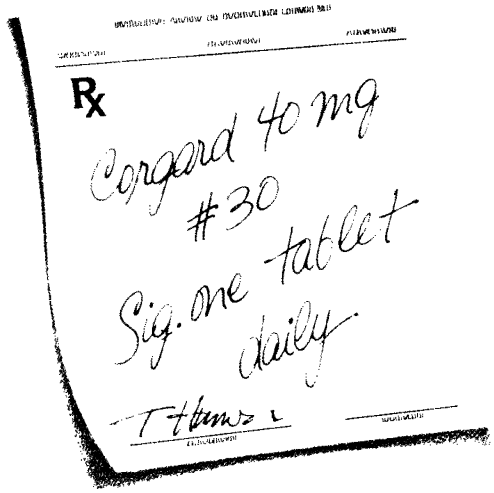
CORGARD®
(nadolol tablets)

40 mg, 80 mg, 120 mg, and 160 mg
easy-to-break scored tablets

ONCE A DAY FOR HYPERTENSION



CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal— Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function—Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions—Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**— Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

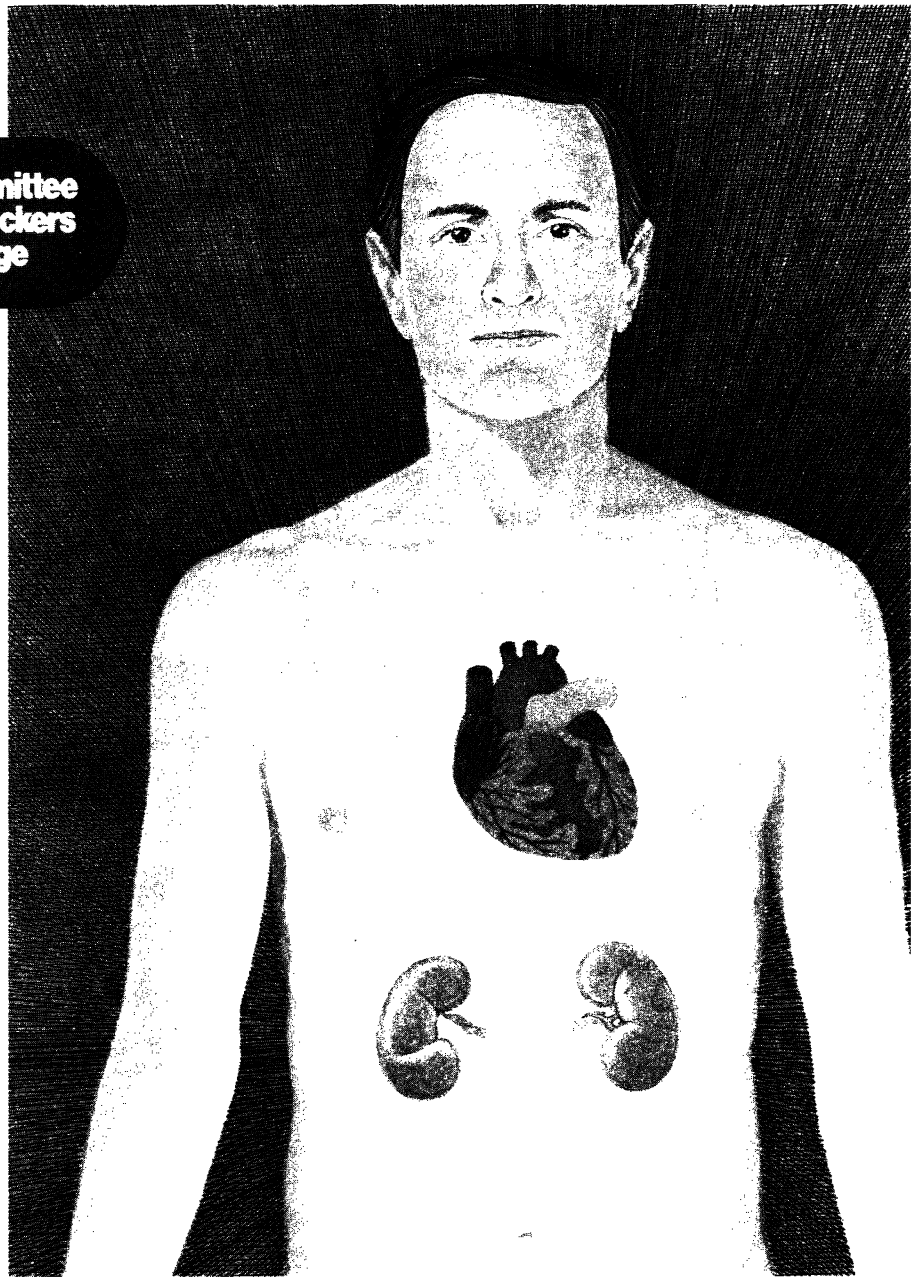
For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

SQUIBB
Innovators in cardiovascular medicine

514-519

Issued: June 1984



The Joint National Committee now advocates beta-blockers for broad Step-1 usage

IN HYPERTENSION
CORGARD®
(nadolol tablets)

BLOCKS BETA RECEPTORS IN THE HEART WHILE APPARENTLY PRESERVING RENAL BLOOD FLOW

Effect on kidney

"...investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function."[1]

"...the majority of investigators utilizing propranolol have reported decrements in RPF [renal plasma flow] and GFR [glomerular filtration rate]..."[1]

CORGARD® (nadolol tablets) should be used with caution in patients with impaired renal function.

Reference: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Mineral Electrolyte Metab 8: 237-254, 1982.

SQUIBB®
Innovators in cardiovascular medicine

TAKE THE ADVANTAGE TO HEART

Please see the adjacent page of this advertisement for brief summary.

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MICRO-TRACER™ ECG PLUS

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A product of space-age miniaturization technology, MICRO-TRACER is a hospital-quality ECG offering greater versatility than any other portable ECG available today.

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Phonocardiogram (PCG) tracings to detect the slightest murmurs, made possible by the accompanying DIF-STET,™ a highly sensitive electronic stethoscope. Up to 12-vector capability. Continuous visual and audible monitoring with a continuous alarm triggered by bradycardia and tachycardia attacks. A heart-rate histogram for monitoring arrhythmias. With its optional modem, remote analyses and consultations can be obtained via the telephone.

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For complete information, write: INTECH Systems Corp., 415 Rabro Drive East, Hauppauge, NY 11788, or call toll-free (800) 854-8376 (outside New York) or call collect (516) 582-8388 (in New York).

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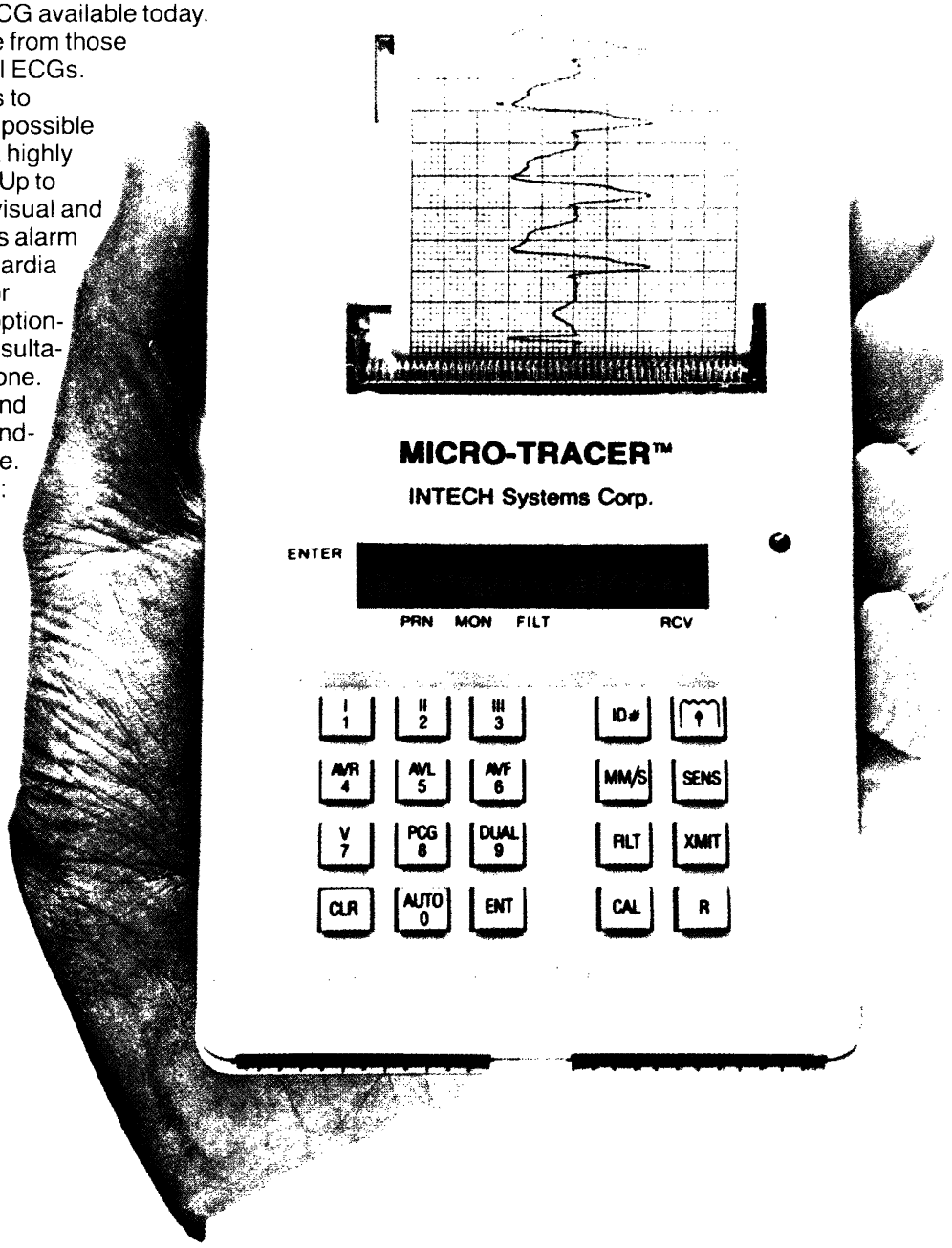

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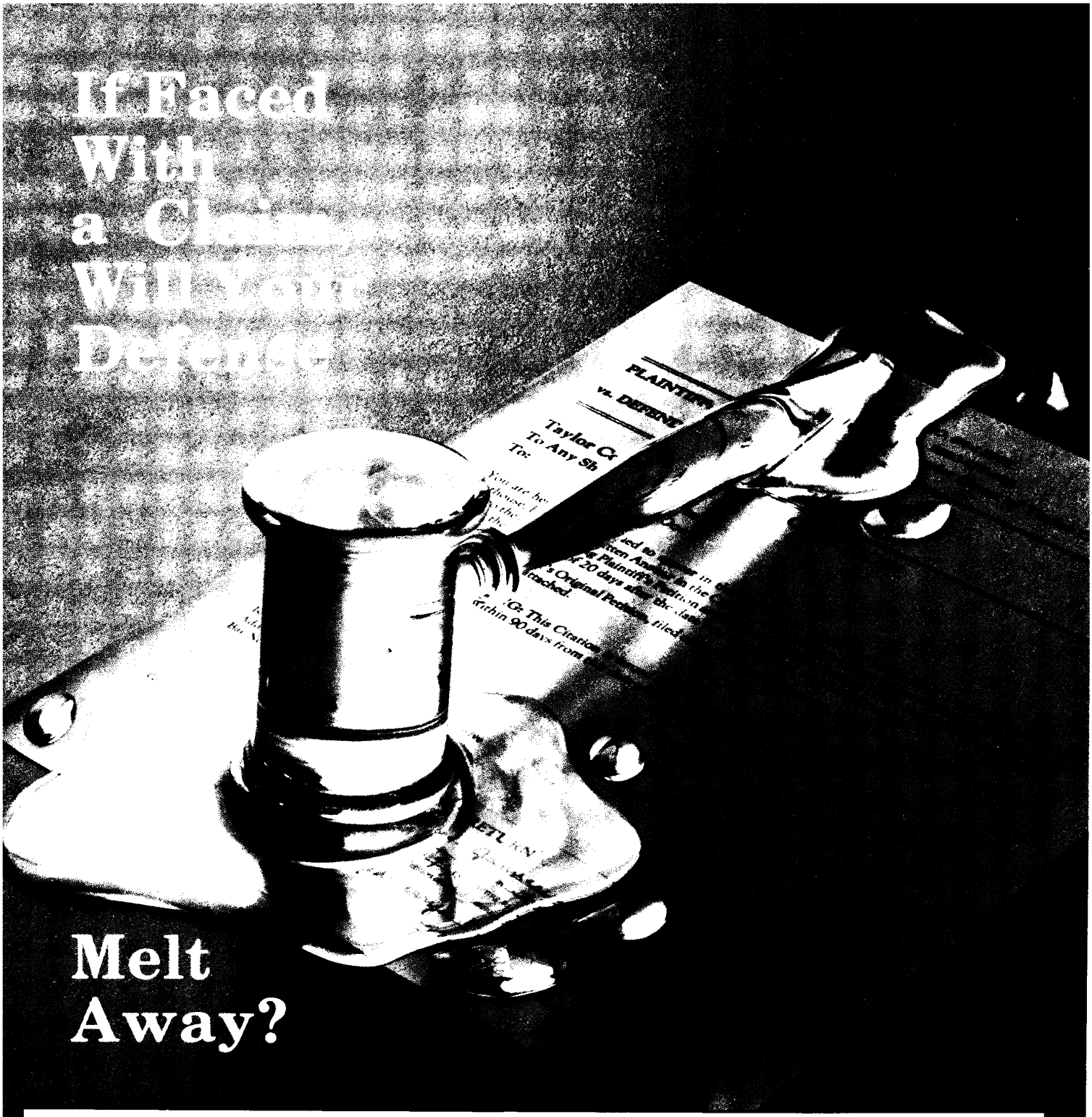

The last concern you need in a malpractice suit is a watered down defense. At Insurance Corporation of America, we believe your reputation as a doctor is your most valuable asset. And we've backed that up with the most aggressive claims defense posture in the business.

Additionally, our "Consent to Settle" clause assures that only *you* can make the decision to settle a claim. With commitments like these, your defense concerns can be put on ice.

For more information, call 1-800-231-2615; in Texas call 1-800-392-9702. Check for availability in your state.

ICA

The Preferred Underwriter

New study reveals no interaction between

Ativan® (lorazepam) and Darvon® (propoxyphene HCl) C-IV

In a study evaluating the influence of propoxyphene coadministration on the pharmacokinetics of the oxidatively metabolized benzodiazepines Xanax® (alprazolam) C-IV and Valium® (diazepam) C-IV, and a benzodiazepine metabolized by conjugation, Ativan® (lorazepam), the following results were reported:

with Xanax, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance.[1]

in the case of Valium, propoxyphene produced a small but not statistically significant impairment of clearance.[1]

propoxyphene had no apparent effect on the distribution, half-life or clearance of Ativan.[1]

In this randomized crossover study, eight healthy male and female volunteers received single oral doses of alprazolam (1 mg), six received single IV doses of diazepam (10 mg), and five received single IV doses of lorazepam (2 mg), once in a drug-free control state and again during coadministration of propoxyphene (65 mg q6h). Consistent with previous findings, this study evidences that Ativan does not interact with drugs that undergo oxidative metabolism.[2-5] In contrast to most other benzodiazepines, Ativan does not compete for the cytochrome P-450 enzyme system.

The clinical implications of the pharmacokinetic interaction, or non-interaction, of propoxyphene with benzodiazepines are not established by this study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

Caution should also be observed when propoxyphene is prescribed for patients who use alcohol to excess.

References

1. Abernethy DR, Greenblatt DJ, Shader RI: Data on file, Wyeth Laboratories.
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3. Abernethy DR, Greenblatt DJ, Divoll M, et al: Psychopharmacology 80:275-278, 1983.
4. Abernethy DR, Greenblatt DJ, Divoll M, et al: N Engl J Med 306:791-792, 1982.
5. Ochs HR, Greenblatt DJ, Abernethy DR: Data on file, Wyeth Laboratories.

Wyeth Laboratories
Philadelphia, PA 19101
TM

Ativan® for (lorazepam) C-IV Anxiety

See important information on following page.

The appearance of these tablets is a registered trademark of Wyeth Laboratories

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) **for** (lorazepam) **Anxiety**

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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Philadelphia, PA 19101

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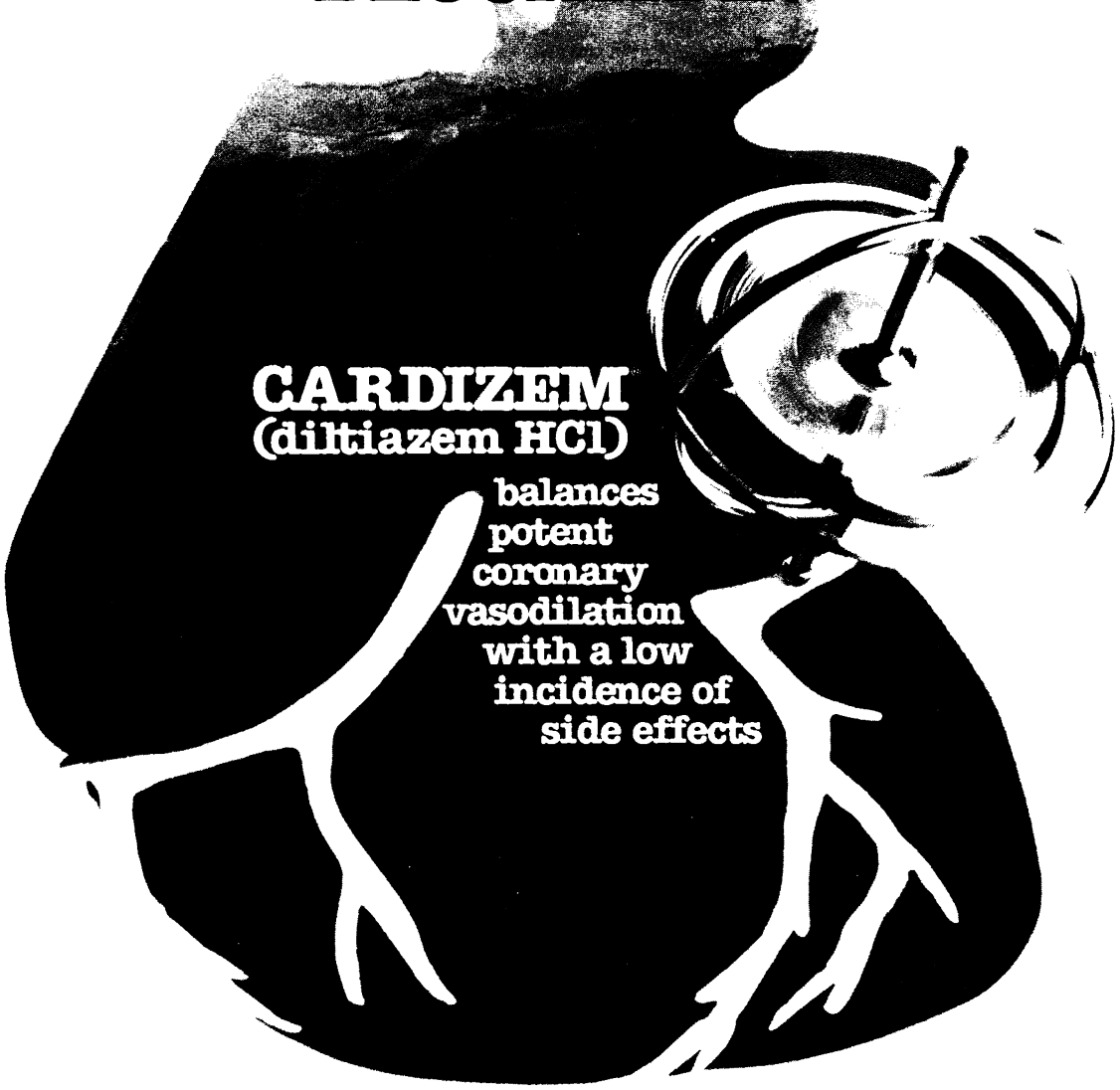
BALANCED CALCIUM CHANNEL BLOCKADE!



Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

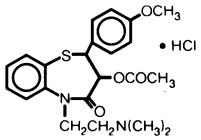
Please see full prescribing information on following page.

PROFESSIONAL USE INFORMATION

Cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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MARION LABORATORIES, INC.
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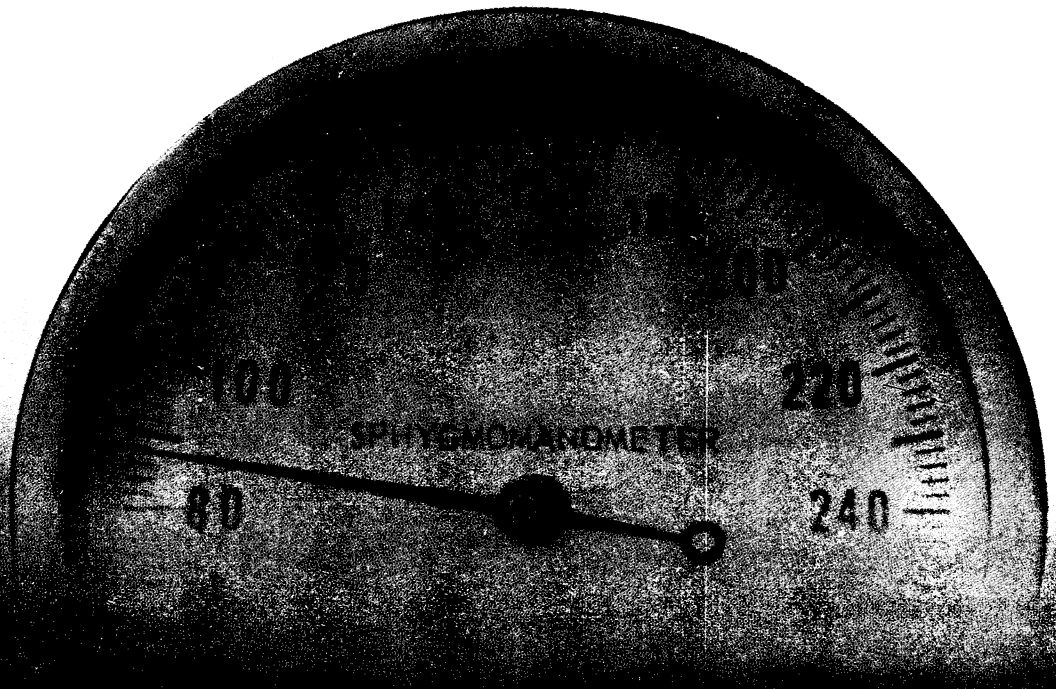
First-step blood pressure control with optimal simplicity

Benefits diuretics cannot offer... Once-daily INDERAL LA (propranolol hydrochloride) with its smooth 24-hour control of blood pressure provides a high degree of patient acceptance without potassium problems, plus the cardiovascular benefits of the world's leading beta blocker.

Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.



Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

80 mg *120 mg* *160 mg*

The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

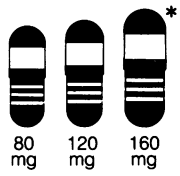
Ayerst

Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement at any given level of effort by blocking the catecholamine-induced increase in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end-systolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in cerebral vessels.

Beta receptor blockade can be useful in conditions in which beta-adrenergic pathology or functional changes, sympathetic activity is detrimental, but also in situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant [illegible] related tumorigenic effects at any of the dosage levels. [illegible] studies with animals did not show any impairment of fertility that was attributable to the [illegible].

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses [illegible] greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: [illegible] adverse effects have been mild and transient and have rarely required withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; [illegible] thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

In clinical anxiety,

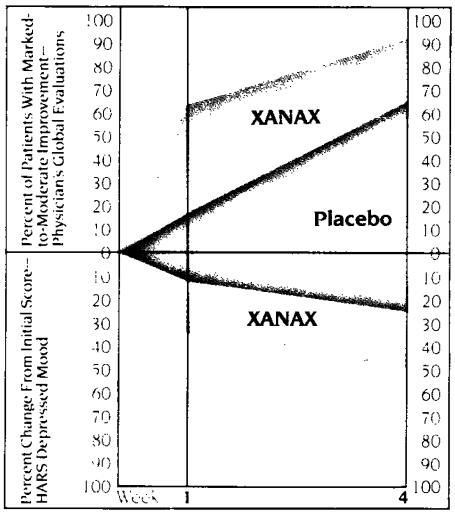
Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

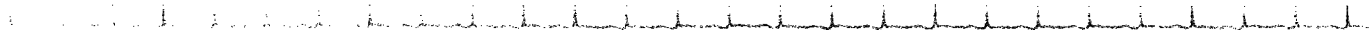
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy

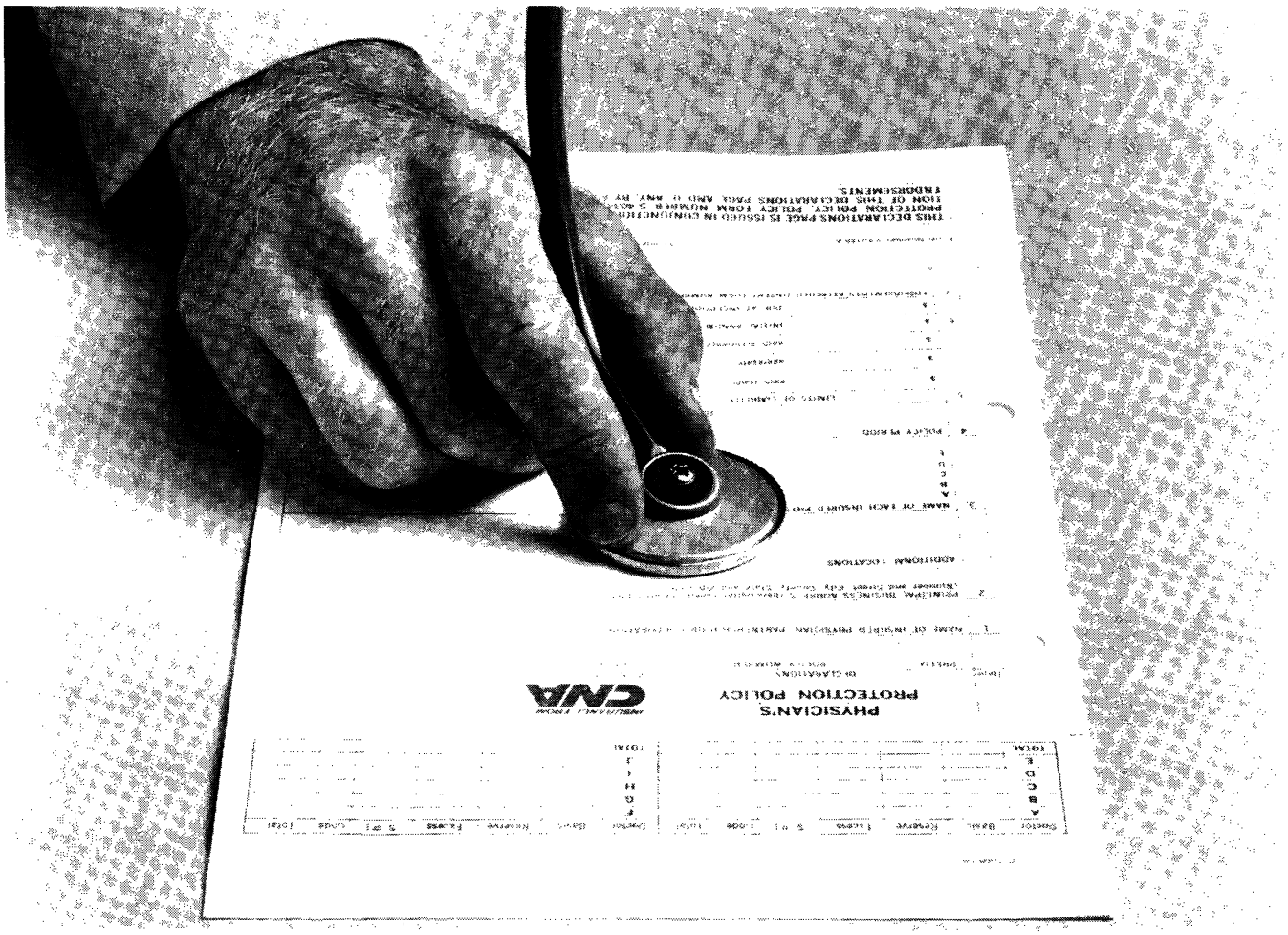


- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets
alprazolam C IV



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the choice would be clear.

You wouldn't settle for anything less than the best possible care to protect the health of your patients. With today's legal climate, why settle for anything less than the best professional liability protection for your practice? The clear choice for medical professional liability protection is the Physicians Protection Program from the CNA Insurance Companies.

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- Vigorous resistance of unfounded malpractice claims—no claim is ever settled without your consent
- 50% premium reduction for new physicians
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- Plus, optional coverages appropriate to your professional and business needs

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Sarah Dore
CNA Insurance Companies
P.O. Box 17369, Denver, Colo. 80217
(303) 759-1500

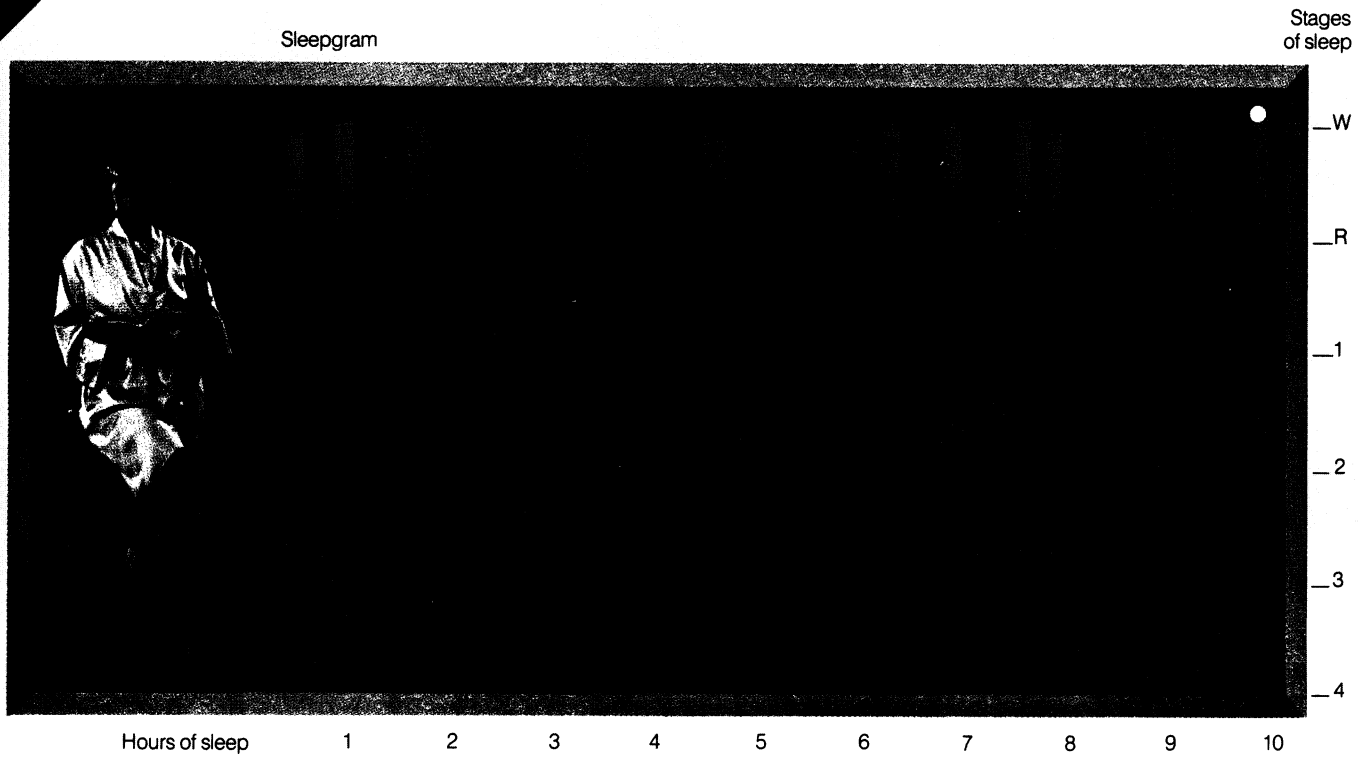
The Physicians Protection Program is underwritten by Continental Casualty Company or CNA Casualty of California, two of the CNA Insurance Companies.

The Physicians Protection Program is available to individual physicians in Washington and Idaho and through association sponsored programs in California.

INSURANCE FROM
CNA
For All the Commitments You Make

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

■ = objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

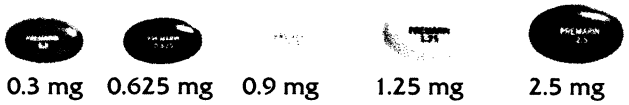
Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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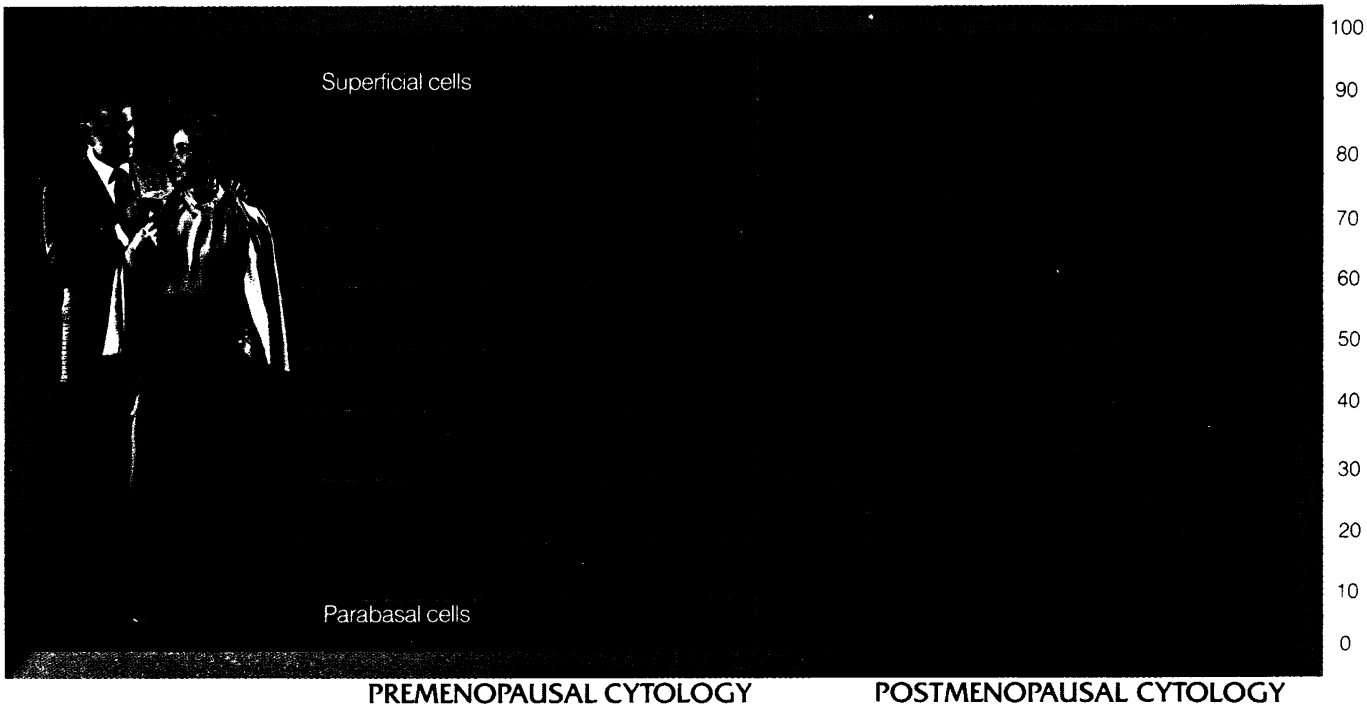
THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

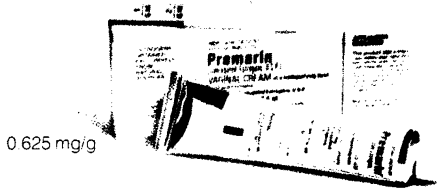
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

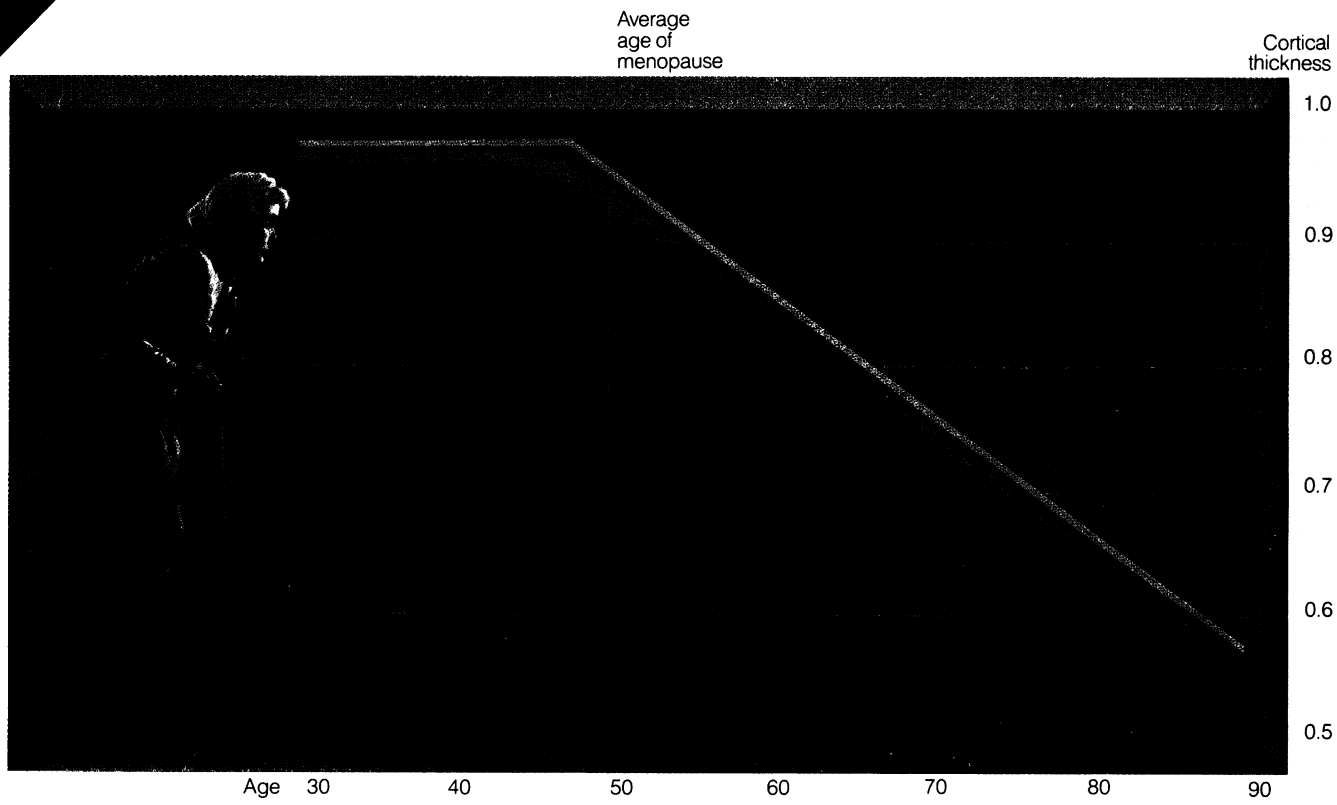
FOR ATROPHIC VAGINITIS

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis.

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogens, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **8934/984**

REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al: Estrogen replacement therapy: Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull.* June 1983, pp 1-5. 4. Ayers LJ: The maturation index: A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G: Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ: Age, estrogen, and bone density. *Clin Obstet Gynecol* 1981;24:203-218. 7. Gordan GS, Picchi J, Roof BS, et al: Postmenopausal osteoporosis. *Am Fam Physician* 1973;8:74-83. 8. US Bureau of the Census. *Statistical Abstract of the United States* 1982-83, ed. 103. Washington, DC, US Dept of Commerce, 1982, p 25. 9. Mallette LE: Osteoporosis: Approaching treatment with optimism. *Postgrad Med* 1982;72:271-278.

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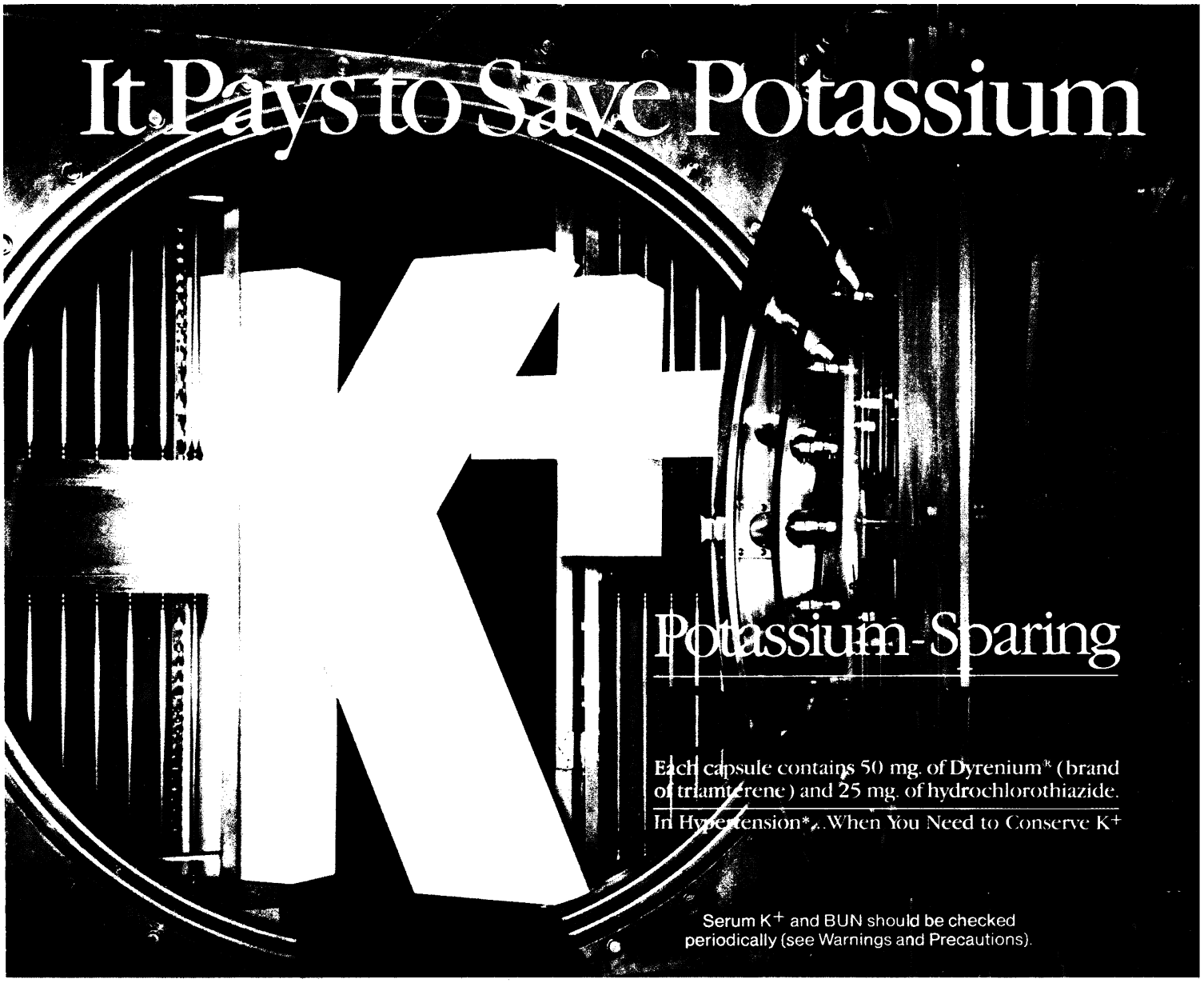

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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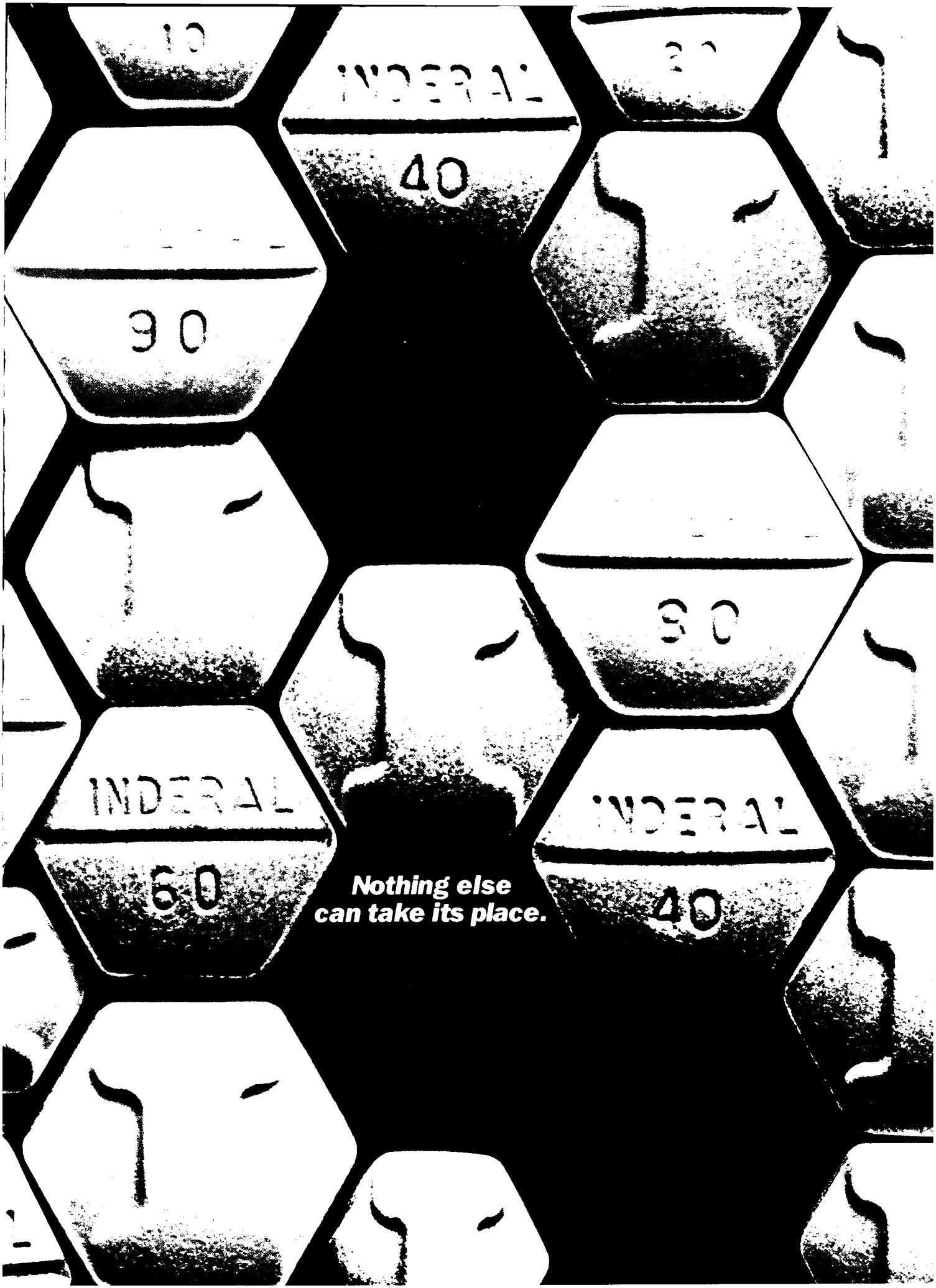
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(PROPRANOLOL HCl)

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure; certain conduction defects; angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL: In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC: Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetics).

PHARMACOKINETIC: A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 vs. 1,024 ng/ml• hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS.

INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

8965/284

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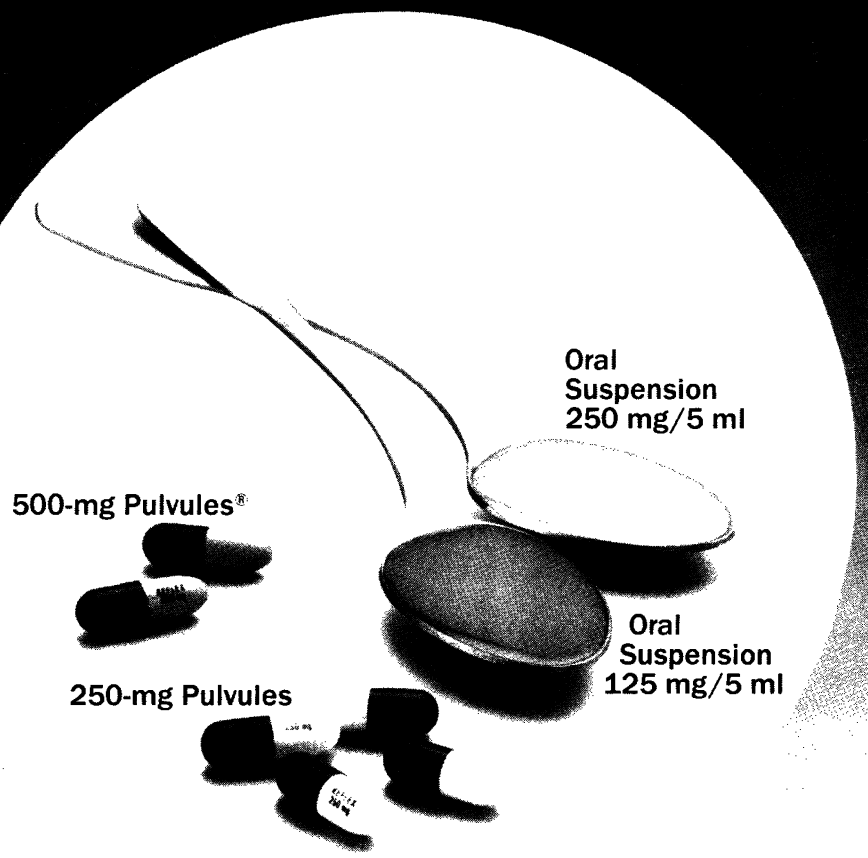

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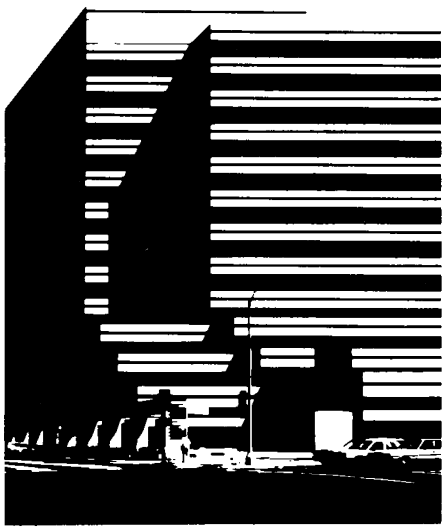

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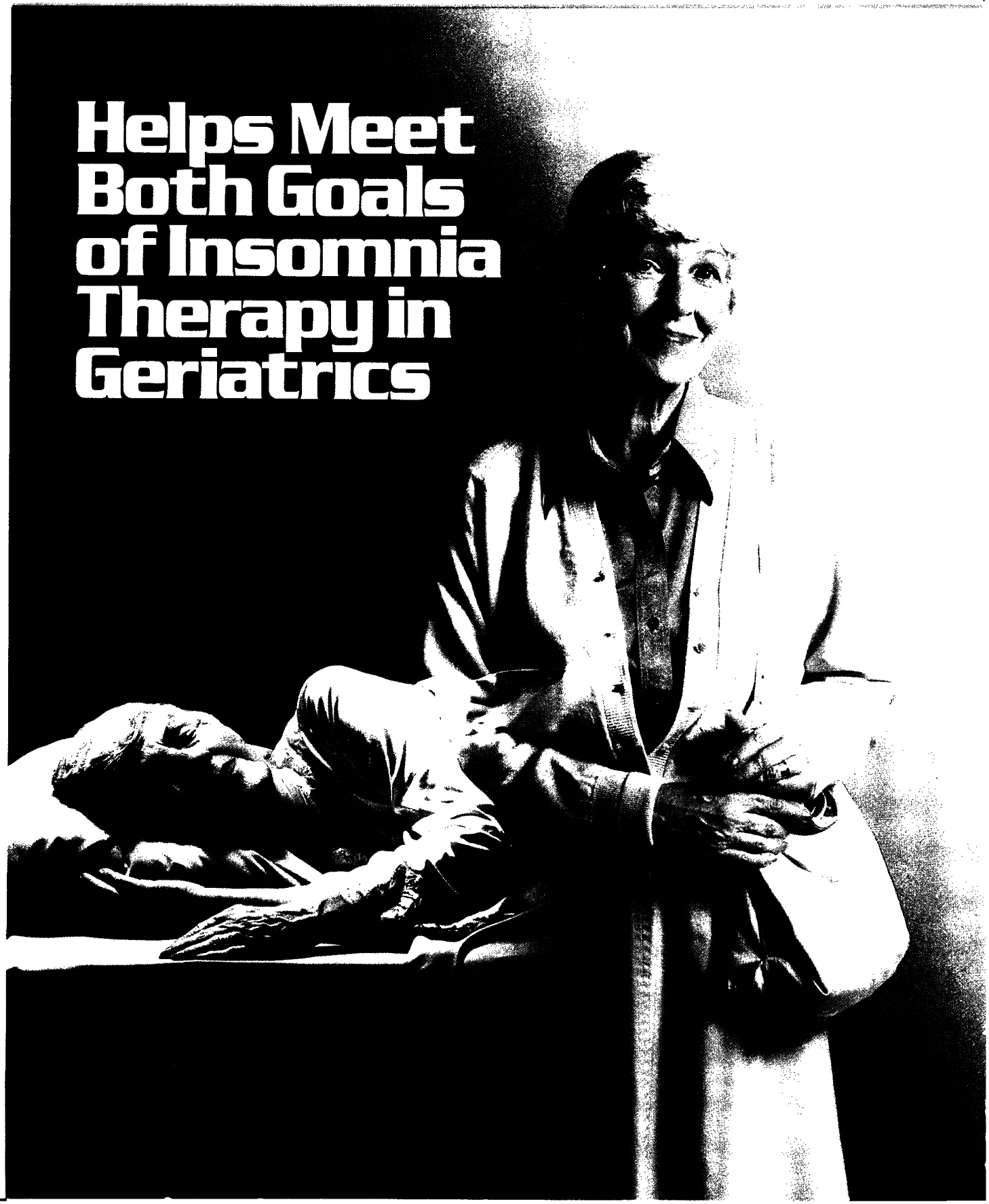

Upjohn Please see next page for brief summary of prescribing information.

Better Initiation and Maintenance of Sleep

Halcion was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.

Peak serum concentration occurs at 1.3 hours.

Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).

Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Better Morning and Daytime Alertness

Halcion has the shortest half-life of any benzodiazepine-derived sleep medication.

In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.

Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.

Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion
triazolam

Halcion Tablets
triazolam IV

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion,* initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam IV

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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PHYSICIANS WANTED

INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

OBSTETRICIAN AND GYNECOLOGIST, Southern California—Leading HMO with 28 facilities, 350,000 members and 370 full-time physicians in Los Angeles and Orange Counties has opportunities for OB/GYN specialists. Excellent compensation and benefits. Send curriculum vitae to Director/Physician Recruitment: CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

CALIFORNIA-URGENT CARE. Positions available for Fall 1984 in free-standing, urgent care settings in several locations. Board certification or eligibility in Emergency Medicine, Family Practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Ave, Suite 500, Oakland, CA 94610, (415) 832-6400.

FAMILY PRACTICE OPPORTUNITY. Established Family Practice group located in SW Washington, 15 minutes from Portland. Flexible scheduling. Full partnership available within one year. Contact E. M. McAninch, MD at (206) 834-3141 or send CV to P.O. Box 1004, Camas, WA 98607.

LA JOLLA, CALIFORNIA-PULMONOLOGIST needed to join pulmonary-critical care group. Salary and later partnership or early buy-in. Must be BE/BC. Send CV to Box 6444, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

UNIVERSITY OF WYOMING STUDENT HEALTH SERVICE—The Student Health Service has an opening for a full-time physician beginning July 1, 1984. The physician must be Board Certified in Family Practice and have approved resident training or have extensive practice experience. Applicant must be licensed in the State of Wyoming and have at least four years of primary care experience. Physician to join three full-time and three part-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, pharmacy and infirmary. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity-Affirmative Action Employer. Send CV to: Dale C. Brentlinger, MD, Director, Student Health Service, University of Wyoming, University Station Box 3068, Laramie, Wyoming 82071.

GENERAL PRACTITIONERS—Specialists—Full-time positions or Locum Tenens. If you're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

FAMILY PRACTITIONER/EMERGENCY PHYSICIAN: MD multispecialty group is seeking second MD to staff urgent care clinic. Partnership potential. Board qualified in Family Practice/Emergency Medicine. Beautiful coastal location. Send CV to James Beckett, MD, Santa Cruz Medical Clinic, 2025 Soquel Avenue, Santa Cruz, CA 95062.

PHYSICIANS WANTED

ORTHOPEDIC SURGEON, Sun Valley, Idaho. Energetic Orthopedic Surgeon to practice with multi-specialty group. Well equipped adjacent hospital. Quality of life high, income moderate. Curriculum vitae and references with first letter please. Dr Lynn T. Levy, PO Box 66, Sun Valley, ID 83353.

FELLOWSHIP IN GENERAL INTERNAL MEDICINE—UCSF/San Francisco General Hospital. Two year program emphasizing clinical research, teaching, patient care and management skills. Available July 1985. Applicants must be Board eligible. Contact Richard J. Haber, MD, Chief, Division of General Internal Medicine 5H22, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110.

FAMILY PHYSICIAN—Board certified or eligible to join the Family Practice Dept. of a growing primary care based, multispecialty group in Northwest Washington. Close to CME and outdoor recreation. Contact Shane Spray, Administrator, Skagit Valley Medical Center, Mt. Vernon, WA 98273; (206) 428-2524.

OCCUPATIONAL PHYSICIAN: Occupational Medicine physician desired for hospital and community based occupational health program. Hospital with over 1,400 employees is located in a medium-sized, highly industrial area in the Northwest that offers excellent schools, recreational and cultural opportunities. Must have clinical skills and administrative experience. Salary based upon experience and qualifications. Contact Ambulatory Care Services, PO Box 2197, Tacoma, WA 98401 or (206) 591-6709.

PHYSICIANS WANTED

OB/GYN—TULARE COUNTY, CALIFORNIA: Board certified/eligible OB/GYN to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas, Los Angeles and San Francisco easily accessed and the Sierra Nevada Mountains nearby. Salary: $85,376-$89,725 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291, (209) 733-6266. An affirmative action employer.

FAMILY PRACITITIONER—TULARE COUNTY, CALIFORNIA: Board certified Family Practitioner to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $78,071-$82,048 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291, (209) 733-6266. An affirmative action employer.

BOARD ELIGIBLE/CERTIFIED SURGEON being recruited by physicians and community to serve the needs of a rural area in beautiful northeastern Washington. Service area of approximately 15,000, solid family practice referral base, sole community hospital/nursing home located in the county seat of Newport, 40 miles north of Spokane. Enjoy the benefits of living year around in a vacationer's paradise, professional satisfaction and the challenge of providing much needed surgical services. Tertiary referral and cross coverage available. Contact David D. Buckman, MD, Chief of Staff or John B. Switzer, Administrator, Newport Community Hospital, Newport, WA 99156.

GASTROENTEROLOGIST: BC or BE, to associate with 4 man internal medicine group in small Northern California city. Modern, complete, endoscopy lab at local hospital. Salary plus percentage. Early partnership, Please send CV to Box 6449, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

A LARGE MULTISPECIALTY REFERRAL CENTER in downtown Seattle will be establishing a major satellite clinic in Federal Way, located 25 miles from the main campus. Well qualified, Board certified or Board eligible physicians in Primary Care areas are encouraged to apply. Send curriculum vitae to: Health Services Consortium, 925 Seneca St., PO Box 1930, Seattle, WA 98111.

FAMILY PRACTICE—Excellent opportunity in New Mexico and Colorado communities for private practice with income quarantee. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

INTERNAL MEDICINE—Excellent opportunity in New Mexico and Colorado communities for private practice with income guarantee. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

WESTERN US, OPENINGS—Several multi-specialty groups and clinics have asked us to recruit physicians for over 50 positions of various specialties. Western States Professional Services, 1551 E. Shaw, #115, Fresno, CA 93710, (209) 226-3363.

(Continued on Page 716)

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(Continued from Page 714)

PHYSICIANS WANTED

INTERNIST-GP/OB-GYN/FP/GP/RADIOLOGIST: For established growing, multi-specialty practice in sunny Los Angeles. Spanish very helpful. First year compensation negotiable. Partnership potential second year. CV to Medical Director, Box 6435, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE: Fellowship in Obstetrics and Family Medicine available July 1, 1985 to June 30, 1986 for qualified FP residency graduate. Opportunity to learn complicated and operative OB while teaching FP residents in beautiful Pacific Northwest. University of Washington faculty appointment, salary and fringes. Send letter and CV: Philip Cleveland, MD, Director, Family Medicine Spokane, S. 511 Pine St., Spokane, WA 99202, (509) 642-2313.

FAMILY PRACTITIONER needed to work as independent contractor on the Monterey Peninsula. Please reply to: Marc Martinez, MD, 8410 Galaxy Circle, Buena Park, CA 90620, (714) 761-3419 or (415) 924-2566.

FAMILY PRACTITIONER—Exceptional opportunity to join five man clinic adjacent to 55 bed acute care hospital. Rural setting in Northern Sacramento Valley. 1 hour from Sacramento, 2 hours from San Francisco and Lake Tahoe. Apply innediately. Send CV to Albert W. Nielsen, MD, Gridley Medical Group, 225 Spruce St., Gridley, CA 95948, (916) 846-5655.

CARDIOLOGIST—Needed now in Southern California, Board certified or eligible to join expanding group. Excellent compensation package. Please send CV to Box 6452, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PATHOLOGIST—The Glennview Pathology Medical Group, with affiliations at six hospitals in the greater Los Angeles area, is looking for a competent Pathologist certified in anatomic and clinical pathology. Applicants should have a desire to grow with the Group, be competent in surgical pathology and interested and able in clinical pathology. Send résumé to: Glenview Pathology Medical Group, 4374 Overland Avenue, Culver City, CA 90230.

OB/GYN: Multi-specialty group in Northwest Washington desires second obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 East Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

ONCOLOGIST/INTERNIST: BC/BE to join eighteen physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 East Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

OTOLARYNGOLOGIST: BC/BE and also interested in facial plastics to join eighteen physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 East Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

OB/GYN for excellent position in San Francisco Bay Area. Multi-specialty group. Contact: Carol Sweig, Western Physicians Registry, 1124 Ballena, Alameda, CA 94501, (415) 521-4110.

ORTHOPEDIC SURGEON for excellent position in San Francisco Bay Area. Multi-specialty group. Contact: Carol Sweig, Western Physicians Registry, 1124 Ballena, Alameda, CA 94501, (415) 521-4110.

ANTERIOR SEGMENT FELLOWSHIP in busy private practice associated with Medical College. Intraocular Lens Implantation, including posterior chamber and anterior chamber lenses. Extracapsular and Phacoemulsification techniques. Argon and Yag Laser. Excellent benefits plus fringes. Send CV and career objectives to: Box 6450, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

BOARD-ELIGIBLE GENERAL INTERNIST for 6-man multi-specialty group in southwestern Colorado. Call: (303) 247-2611 or send CV to Bonnie DuPuis, PO Box 2637, Durango, CO 81301.

SACRAMENTO: Full-time positions available for Board-prepared or Board-certified Emergency Physicians with established multi-hospital group practicing in the Sacramento Valley. Group organized as partnership with competitive salary and benefits. Malpractice paid. All hospitals with moderate volumes, many act as EMS base-stations. Send CV to Sacramento Emergency Medical Group, PO Box 214584, Sacramento, CA 95821.

PHYSICIANS WANTED

SOUTH DAKOTA: Expanding physician-owned group has opening for full-time career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436, or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

WYOMING: Residency-trained or Board-prepared physician (preferred) for busy emergency department. Physician-owned group with malpractice, disability, health insurance, profit sharing, etc. Excellent hunting, fishing, skiing, etc., nearby. Contact Donald Kougl, MD, (307) 632-1436, or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career oriented Emergency Physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436, or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

UNEXPECTED OPPORTUNITY FOR INTERNIST to associate with three busy internists in suburban community 20 minutes east of San Francisco. Reply with CV to Box 6443, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTITIONER, BC/BE. Full-time position available with community clinic in beautiful family area near San Francisco. Excellent benefits and working conditions. Call and OB included. Call Arturo Ray (415) 471-5907 or send CV to Tiburcio Vasquez Health Center, 33255 Ninth St., Union City, CA 94587.

FAMILY PRACTITIONER BC/BE needed for large multi-specialty clinic in San Francisco Bay area. Competitive salary first year, with excellent benefits. Eligible for full partnership after one year. Send résumé to Administrator, San Jose Medical Group, 45 South 17th St., San Jose, CA 95112.

LOCUM TENENS

GENERAL RADIOLOGIST seeks ½-time position in South Bay (S.F.). Experienced in routine diagnostic studies plus industrial injury—acute care cases. Reply to Box 6442, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

LOCUM TENENS NEEDED—FP for busy practice with emphasis on Obstetrics. Needed for 4 months beginning December 1, 1984. Contact Judith Babcock, MD, 7935 216th St. S.W. Suite E, Edmonds, WA 98020; (206) 775-0681.

WORK PART TIME: Position available for Internist or GP with Internal Medicine experience to work at Primary Care Practice in Northern California Sierra foothills community of 25,000, 70 miles North of Sacramento. Share rotating practice with two other MD's; you work 1 week in 3. Out-patient and in-patient responsibilites in modern, fully equipped hospital. Minimum salary of $2,000/week plus incentives. Insurance and housing provided. Send CV and references to: David Lomba, Business Manager, 133 'A' Ascot Ct., Moraga, CA 94556.

PRACTICE WANTED

BOARD CERTIFIED RADIOLOGIST, 32, presently in aggressive hospital practice, wishes to purchase or associate in quality office practice in a coastal Northern California, Pacific Northwest or Bay area community. Call (714) 645-2393.

SITUATIONS WANTED

UCLA GRADUATE/UNM IMR3 available July 1985 for 5-10 physician Internal Medicine group practice in Northern California-Oregon. Interests in ICU and computers (publication accepted). Contact: Marc Gelman, MD, 2901 Euclid, #24D, Albuquerque, NM 87106.

PRACTICES AVAILABLE

DERMATOLOGY—Southern California, Practice for sale. Established practice in prestigious county. Gross $193K. Beautiful 1,500 sq. ft. suite. Full price $125K. Professional Practice Sales (714) 832-0230.

SAN FRANCISCO PARTNERSHIP: New primary care clinic fifteen minutes from the heart of downtown San Francisco seeks BE/BC Primary Care Physician. No buy-in, guaranteed base compensation and incentive, regular hours. Ideal for physician who wants private practice setting with strong management and financial support. Send CV to: Michael Goluska, MD, 2200 Sixth Ave., Suite 1200-BB, Seattle, WA 98121, (206) 624-6888.

CALIFORNIA NEAR SAN JOSE. active Family Practice, well equipped office to rent or buy; accredited hospital, plan retirement. Write Box 6424, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WELL ESTABLISHED FAMILY PRACTICE AND CLINIC FOR SALE. 1,600 square feet, well equipped with laboratory, x-ray and surgery. Will negotiate terms. Contact J. Erickson, MD, Box 44488, Tacoma, WA 98444.

WESTERN WASHINGTON—Private practices available in OB/GYN, Pulmonary, Internal Medicine and Family Practice. For details, contact Eloise Gusman, 1 (800) 535-7698 or send CV to 2800 Veterans Blvd., Suite 170, Metairie, LA 70002. Our service is completely confidential and offered at no cost or obligation.

CALIFORNIA—Radiology, Ophthalmology, Ob/Gyn, Family, Internal, Surgery, Occupational Med., Pediatric, Orthopedic, Psychiatry, Dermatology, others. Contact; Mary Bradshaw, Practice Broker/Recruiter, 21 Altamount, Orinda, CA 94563, (415) 376-0762.

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FAMILY PHYSICIAN RETIRING and wishes to sell practice. Located in heart of Puget Sound country. Town located near excellent hospital and Seattle. T. T. Middleton, MD, PO Box 145, Port Orchard, WA 98366, (206) 876-8051.

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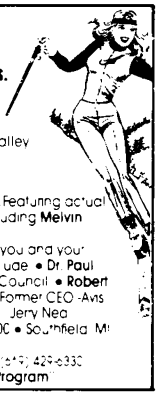

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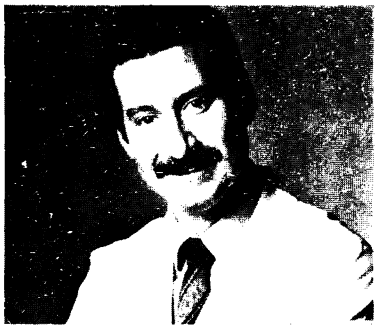

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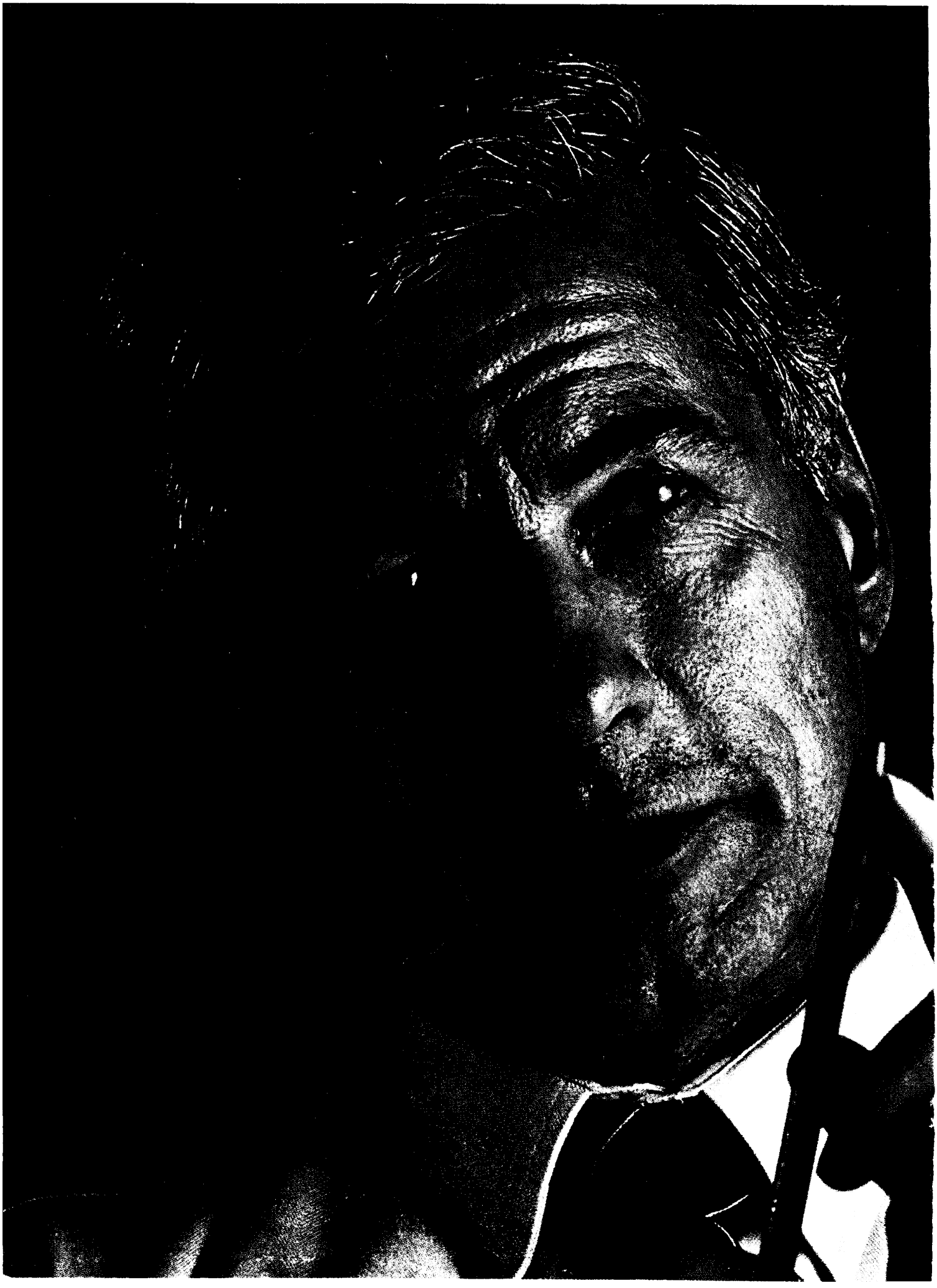

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Please see next page for brief summary of prescribing information.

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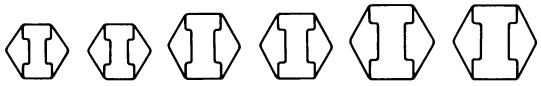


10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure; certain conduction defects; angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL: In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC: Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC: A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 *vs.* 1,024 ng/ml• hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS.

INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

9371/1184

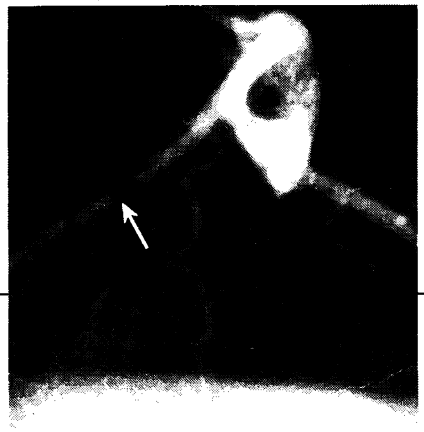
Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

When anxiety and organic disease are paired...

TROUBLED HEART

A

An obstructed coronary artery suggests the heart is already troubled—or soon will be. In most cases, the obstruction proves to be an atherosclerotic plaque. At other times—as in this case—the "blockage" stems largely from sudden spasmodic contractions of the arterial wall. In the photos shown here—taken during the catheterization of a cardiac patient—you can see an actual coronary artery spasm in progress: (A) the coronary artery as it is at baseline; (B) the spontaneous narrowing of the vessel (arrow) to a 75% obstruction; and (C) subsidence of the spasm after intracoronary nitroglycerin.



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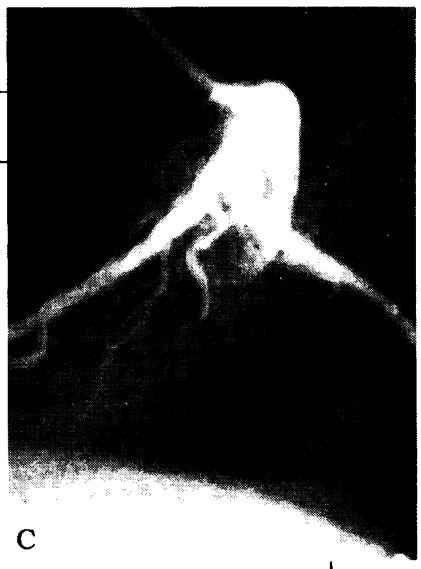

C

ROCHE

TROUBLED PATIENT

Disturbed by anginal pain, worried about what *could* happen—the cardiac patient may go through periods when anxiety symptoms and apprehension threaten to become unmanageable. At such times, a short course of Valium (diazepam/Roche) can offer substantial relief of acute anxiety. Valium works promptly: Patients usually feel distinctly calmer in hours, report pronounced and sustained relief of anxiety within days. Helpful, too—adding an *h.s.* dose of Valium to the usual *t.i.d.* schedule can help relieve excessive nighttime anxiety.

An especially important benefit of Valium is that it is well tolerated by most cardiac patients. Side effects more serious than drowsiness, fatigue or ataxia are rare. Patients should be cautioned against drinking alcohol or driving while taking Valium. Periodic reassessment of the need for anxiolytic treatment is also recommended.

Unsurpassed in the treatment of anxiety symptoms

VALIUM®(IV)
diazepam/Roche
scored tablets

Note our distinctive look

2 mg 5 mg 10 mg

The cut out "V" design is a trademark of Roche Products Inc.

Please see summary of product information on following page.

Don't Miss The Boat

Reserve space now! Here's your ticket to the California Medical Association's 114th Annual Session, March 8—13, 1985, Town and Country Hotel, San Diego. Send for the Annual Session Tabloid which includes complete program and registration information. Mail this form to:

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Attention: Robert Sparacino
California Medical Association
44 Gough Street
San Francisco, CA 94103

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A new low price for Motrin ibuprofen

Motrin is priced lower than Clinoril, Feldene, or Naprosyn.

The price of *Motrin* Tablets to pharmacies has been reduced as much as 35%. Patients taking the average dosage should now pay less for therapy with *Motrin* Tablets than for almost any other nonsteroidal anti-inflammatory drug you prescribe...less, for example, than for Clinoril, Feldene, or Naprosyn.

New low price means major savings.

The dramatic reduction in the price of *Motrin* Tablets means substantial savings from now on for your patients and for patients all across the country for whom *Motrin* Tablets are prescribed. And, of course, all strengths of *Motrin* Tablets continue to be available by prescription only.

Please see the following page for a brief summary of prescribing information.

Motrin® 400 & 600 mg TABLETS
ibuprofen

Good medicine...good value

The Upjohn Company Upjohn Kalamazoo, Michigan 49001

Doctors Won Independence With SCPIE

The situation was grim in 1975.
The cost of professional liability insurance had skyrocketed nearly 500% in 6 years. Most commercial carriers quit the field, and those remaining wanted more than doctors and their patients could pay.

Bombarded by nuisance lawsuits and runaway jury verdicts, doctors faced an historic crisis.

That's when the Spirit of '75 took hold.
Doctors fought back—and won!
First, the Legislature passed a law to control lawsuit mania.

Then came the real key to victory—physicians organized their own insurance company—SCPIE.

Today, physician policyholders own SCPIE, they run it and they realize any profits.

The battle isn't over. SCPIE's success attracts many predators. But physicians will keep their independence as long as they support their company.

That's the Spirit of '75!

scpie

Sponsored by SOCAP: The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County and Ventura County.

Southern California Physicians Insurance Exchange, 2029 Century Park East, Los Angeles, CA 90067 (213) 552-8900

Improving the outlook... in mixed depression and anxiety

A rational approach, combining

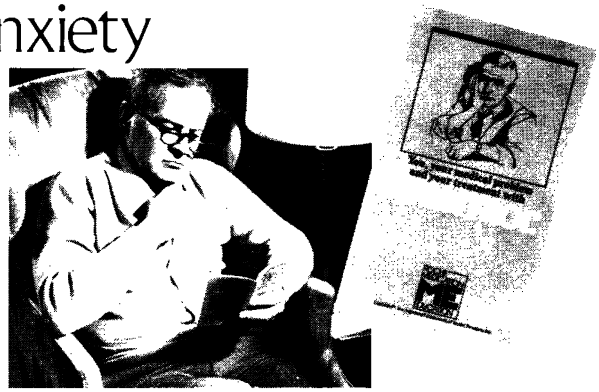
- The standard antidepressant: amitriptyline
- The proven anxiolytic: Librium® (chlordiazepoxide HCl/Roche)Ⓒ Ⓥ

Marked improvement often occurs as early as the first week.

Headache, insomnia or GI upsets associated with mixed depression and anxiety often respond quickly.

Feeling better, patients feel encouraged to stay the course—therefore, fewer dropouts due to side effects: $p < 0.006$ compared to amitriptyline.* Patients should be cautioned about the combined effects of Limbitrol with alcohol and other CNS depressants, and about activities requiring complete mental alertness such as operating machinery or driving a car.

*Feighner JP: Psychopharmacology 61: 217-225, Mar 22, 1979.



A Roche Medication Education Booklet—
"You, your medical problem and your treatment with Limbitrol."

Valuable adjunct to dual therapy with Limbitrol:

Because an informed patient is more responsive...

This easy-to-read brochure explains the rationale of dual therapy with Limbitrol and encourages patient compliance. To obtain a complimentary supply, please contact your Roche representative.

In moderate depression and anxiety

Limbitrol® Ⓒ Ⓥ

Tablets 5-12.5 -

Tablets 10-25 -

Rapid clearing through dual action

LIMBITROL® Tablets Ⓒ Ⓥ
Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose* packages of 100; Prescription Paks of 50.

ROCHE®

ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

CLEARING BOTH THE DEPRESSION & THE ANXIETY

ROCHE

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

Please see summary of product information on reverse side.